

Exhibit A [Second Supplemental Amendment (Following Applicants' June 14, 2001
Amendment For The Purpose Of Claim Consolidation) -- July 12, 2001]

1700. (Twice Amended) A process for determining the sequence of a nucleic acid of interest, comprising the steps of:

providing or generating non-radioactive labeled nucleic acid fragments, each fragment comprising a sequence complementary to said nucleic acid of interest or a portion thereof, wherein each of said fragments comprises one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, wherein said detectable non-radioactive modified or labeled nucleotides or nucleotide analogs comprise one or more chelating compounds or chelating components capable of chelating a [radioactive] metal or metal ion and providing a detectable [radioactive] signal, and wherein said one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety, or the base analog thereof;

subjecting said labeled fragments to a sequencing gel to separate or resolve said fragments; and

detecting the presence of each of said separated or resolved fragments by means of the detectable [radioactive] signal provided by a [radioactive] metal or metal ion chelated by said chelating compounds or chelating components in the detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, and determining the sequence of said nucleic acid of interest.

Filed: June 7, 1995

Marked-Up Version Of The Amended Claims

Page 2 [Exhibit A To Second Supplemental Amendment (Following Applicants'

June 14, 2001 Amendment For The Purpose Of Claim Consolidation)

-- July 12, 2001]

1701. (Thrice Amended) A process for determining the sequence of a nucleic acid of interest, comprising the steps of:

providing or generating detectable non-radioactive labeled nucleic acid fragments, each fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, wherein said detectable non-radioactive modified or labeled nucleotides or nucleotide analogs comprise one or more chelating compounds or chelating components capable of chelating a ~~radioactive~~ metal or metal ion and providing a detectable ~~radioactive~~ signal, and wherein said one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety, or the base analog thereof;

introducing or subjecting said fragments to a sequencing gel;
separating or resolving said fragments in said sequencing gel; and
detecting each of the separated or resolved fragments by means of the detectable ~~radioactive~~ signal provided by a ~~radioactive~~ metal or metal ion chelated by said chelating compounds or chelating components in the detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, and determining the sequence of said nucleic acid of interest.

Filed: June 7, 1995

Marked-Up Version Of The Amended Claims

Page 3 [Exhibit A To Second Supplemental Amendment (Following Applicants'

June 14, 2001 Amendment For The Purpose Of Claim Consolidation)

-- July 12, 2001]

1702. (Thrice Amended) A process for determining the sequence of a nucleic acid of interest, comprising the steps of:

providing or generating detectable non-radioactive labeled nucleic acid fragments, each fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, wherein said detectable non-radioactive modified or labeled nucleotides or nucleotide analogs comprise one or more chelating compounds or chelating components capable of chelating a [radioactive] metal or metal ion and providing a detectable [radioactive] signal, and wherein said one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety or the base analog thereof;

[radioactively] detecting with a sequencing gel the detectable non-radioactive labeled nucleic acid fragments by means of a [radioactive] metal or metal ion chelated by said chelating compounds or chelating components; and determining the sequence of said nucleic acid of interest.

Filed: June 7, 1995

Marked-Up Version Of The Amended Claims

Page 4 [Exhibit A To Second Supplemental Amendment (Following Applicants'

June 14, 2001 Amendment For The Purpose Of Claim Consolidation)

-- July 12, 2001]

1703. (Thrice Amended) A process for determining the sequence of a nucleic acid of interest, comprising the step of detecting with a sequencing gel one or more detectable non-radioactive labeled nucleic acid fragments comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, wherein said detectable non-radioactive modified or labeled nucleotides or nucleotide analogs comprise one or more chelating compounds or chelating components capable of chelating a [radioactive] metal or metal ion and providing a detectable [radioactive] signal, and wherein said one or more detectable non-radioactive modified nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the base moiety or the base analog thereof.

1704. (Thrice Amended) A process for determining in a sequencing gel the presence of nucleic acid fragments comprising a sequence complementary to a nucleic acid sequence of interest or a portion thereof, said process comprising the steps of:

(A) providing

(i) one or more detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into a nucleic acid, or

Filed: June 7, 1995

Marked-Up Version Of The Amended Claims

Page 5 [Exhibit A To Second Supplemental Amendment (Following Applicants'

June 14, 2001 Amendment For The Purpose Of Claim Consolidation)

-- July 12, 2001]

(ii) one or more oligonucleotides or polynucleotides comprising at least one of said detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs; or

(iii) both (i) and (ii);

wherein said detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs (i) and said oligonucleotides and polynucleotides (ii) are capable of attaching to or coupling to or incorporating into or forming one or more nucleic acid fragments, wherein said detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs comprise one or more chelating compounds or chelating components capable of chelating a [radioactive] metal or metal ion and providing a detectable [radioactive] signal, and wherein said detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs have been modified non-disruptively or disruptively on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety or the base analog thereof; and;

(B) incorporating said one or more detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs (i) or said one or more oligonucleotides or polynucleotides comprising at least one of said detectable non-radioactive chemically modified or labeled nucleotides (ii), or both (i) and (ii), into said one or more nucleic acid fragments, to prepare detectable non-radioactive labeled fragments, each such fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, said detectable non-radioactive labeled fragments further comprising one or more detectable non-radioactive chemically modified nucleotides or nucleotide analogs selected

Filed: June 7, 1995

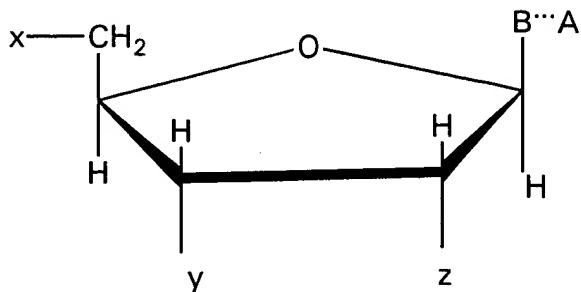
Marked-Up Version Of The Amended Claims

Page 6 [Exhibit A To Second Supplemental Amendment (Following Applicants'

June 14, 2001 Amendment For Th Purpose Of Claim Consolidation)

-- July 12, 2001]

from the group consisting of:



wherein B represents a purine moiety, a 7-deazapurine moiety, a pyrimidine moiety, or an analog of any of the foregoing, and B is covalently bonded to the C1'-position of the sugar moiety or sugar analog, provided that whenever B is a purine, a purine analog, a 7-deazapurine moiety or a 7-deazapurine analog, the sugar moiety or sugar analog is attached at the N9 position of the purine moiety, the purine analog, the, 7-deazapurine moiety or the 7-analog thereof, and whenever B is a pyrimidine moiety or a pyrimidine analog, the sugar moiety or sugar analog is attached at the N1 position of the pyrimidine moiety or the pyrimidine analog;

wherein A comprises at least three carbon atoms and represents at least one component of a signalling moiety comprising a chelating compound or chelating component capable of chelating a [radioactive] metal or metal ion and providing directly or indirectly a detectable [radioactive] signal; and

wherein B and A are covalently attached directly or through a linkage group, and

Filed: June 7, 1995

Marked-Up Version Of The Amended Claims

Page 7 [Exhibit A To Second Supplemental Amendment (Following Applicants' June 14, 2001 Amendment For The Purpose Of Claim Consolidation)
-- July 12, 2001]

wherein x comprises a member selected from the group consisting of:

O	O	O	O	O	O	O
H-;HO-; -O-P-O-;HO-P-O-;HO-P-O-P-O-;HO-P-O-P-O-P-O-						
OH	OH	OH	OH	OH	OH	OH

wherein y comprises a member selected from the group consisting of:

O	O	O	O	O	O	O
H-;HO-; -O-P-O-;HO-P-O-;HO-P-O-P-O-;HO-P-O-P-O-P-O-						
OH	OH	OH	OH	OH	OH	OH

wherein z comprises a member selected from the group consisting of
H- and HO-

(ii)

Sig

|

PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Filed: June 7, 1995

Marked-Up Version Of The Amended Claims

Page 8 [Exhibit A To Second Supplemental Amendment (Following Applicants'

June 14, 2001 Amendment For The Purpose Of Claim Consolidation)

-- July 12, 2001]

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a [radioactive] metal or metal ion and providing a detectable [radioactive] signal, and
wherein said PM is covalently attached to SM, said BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii)

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog,

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a [radioactive] metal or metal ion and providing a detectable [radioactive] signal; and

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

(C) transferring or subjecting said labeled fragments to a sequencing gel;

(D) separating or resolving said labeled fragments; and

(E) detecting directly or indirectly the presence of said labeled

Filed: June 7, 1995

Marked-Up Version Of The Amended Claims

Page 9 [Exhibit A To Second Supplemental Amendment (Following Applicants'

June 14, 2001 Amendment For The Purpose Of Claim Consolidation)

-- July 12, 2001]

fragments by means of a [radioactive] metal or metal ion chelated by said chelating compounds or chelating components.

1705. (Twice Amended) A process for detecting a nucleic acid of interest in a sample, which process comprises the steps of:

(a) specifically hybridizing said nucleic acid of interest in the sample with one or more oligo- or polynucleotides, each such oligo- or polynucleotide being complementary to or capable of hybridizing with said nucleic acid of interest or a portion thereof, wherein said oligo- or polynucleotides comprise one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said detectable non-radioactive modified or labeled nucleotides or nucleotide analogs are selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety or a base analog of any of the foregoing; and

Filed: June 7, 1995

Marked-Up Version Of The Amended Claims

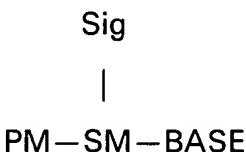
Page 10 [Exhibit A To Second Supplemental Amendment (Following Applicants'

June 14, 2001 Amendment For The Purpose Of Claim Consolidation)

-- July 12, 2001]

Sig is a signaling moiety comprising a chelating compound or component capable of chelating a [radioactive] metal or metal ion and providing a detectable [radioactive] signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE directly or through a linkage group at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof, and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization;

(ii) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or component capable of providing chelating a [radioactive] metal or metal ion and a detectable [radioactive] signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage

Filed: June 7, 1995

Marked-Up Version Of The Amended Claims

Page 11 [Exhibit A To Second Supplemental Amendment (Following Applicants'

June 14, 2001 Amendment For The Purpose Of Claim Consolidation)

-- July 12, 2001]

group and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization; and

(iii) a nucleotide or nucleotide analog, said nucleotide having the formula

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or components capable of chelating a [radioactive] metal or metal ion and providing a detectable [radioactive] signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group, and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization;

provided that when said nucleotide or nucleotide analog (iii) is attached to an oligoribonucleotide or a polyribonucleotide, and provided that when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a [2',3'] 2', 3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide; and

Filed: June 7, 1995

Marked-Up Version Of The Amended Claims

Page 12 [Exhibit A To Second Supplemental Amendment (Following Applicants'

June 14, 2001 Amendment For The Purpose Of Claim Consolidation)

-- July 12, 2001]

(b) detecting radioactively the presence of said signaling moieties Sig in any of the [oligo- or] oligo- or polynucleotides which have hybridized to said nucleic acid of interest by means of a [radioactive] metal or metal ion chelated by said chelating compounds or chelating components.

1706. (Twice Amended) A process for detecting a nucleic acid of interest in a sample, which process comprises the steps of:

(A) providing:

- (i) an oligo- or polynucleotide having two segments:
 - (a) a first segment complementary to and capable of hybridizing to a portion of said nucleic acid of interest; and
 - (b) a second segment comprising at least one protein binding sequence; and
- (ii) a detectable protein capable of binding to said protein binding sequence and comprising a chelating compound or chelating component capable of chelating a [radioactive] metal or metal ion and providing a detectable [radioactive] signal;

(B) contacting a sample suspected of containing said nucleic acid of interest with said oligo- or polynucleotide (i) and said detectable protein (ii) to form a complex;

(C) detecting [radioactively] the presence of said protein in said complex and said nucleic acid of interest by means of a [radioactive] metal or metal ion chelated by said chelating compound or chelating component.

Filed: June 7, 1995

Marked-Up Version Of The Amended Claims

Page 13 [Exhibit A To Second Supplemental Amendment (Following Applicants'

June 14, 2001 Amendment For The Purpose Of Claim Consolidation)

-- July 12, 2001]

1707. (Thrice Amended) A process for determining whether the number of copies of a particular chromosome in a cell is normal or abnormal, the process comprising the steps of:

contacting said cell under hybridizing conditions with one or more clones or DNA fragments, or oligo- or polynucleotides derived from said clone or clones, wherein said clones or fragments or oligo- or polynucleotides are capable of hybridizing specifically to a locus or loci of said particular chromosome or a portion thereof, wherein said clones or fragments or oligo- or polynucleotides comprise one or more detectable non-radioactive modified or labeled nucleotides or nucleotide [analogs], which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said detectable non-radioactive modified or labeled nucleotides or nucleotide analogs are selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety or an analog of any of the foregoing thereof, and

Filed: June 7, 1995

Marked-Up Version Of The Amended Claims

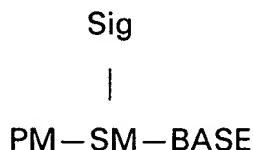
Page 14 [Exhibit A To Second Supplemental Amendment (Following Applicants'

June 14, 2001 Amendment For The Purpose Of Claim Consolidation)

-- July 12, 2001]

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a [radioactive] metal or metal ion and providing a detectable [radioactive] signal, wherein PM is covalently attached to the SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof, and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;

(ii) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a [radioactive] metal or metal ion and providing a detectable [radioactive] signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

Filed: June 7, 1995

Marked-Up Version Of The Amend d Claims

Page 15 [Exhibit A To Second Supplemental Amendment (Following Applicants'

June 14, 2001 Amendment For The Purpose Of Claim Consolidation)

-- July 12, 2001]

(iii) a nucleotide or nucleotide analog having the formula

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a [radioactive] metal or metal ion and providing a detectable [radioactive] signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group, to permit specific hybridization of said clone or clones or DNA fragments or oligo- or polynucleotides to the locus or loci of said particular chromosome;

detecting [radioactively] the signal generated by said specifically hybridized clone or clones or DNA fragments or oligo- or polynucleotides by means of a [radioactive] metal or metal ion chelated by said chelating compound or chelating component, and determining the number of copies of said particular chromosome; and

comparing said determined number of copies of said particular chromosome with a number of copies of said particular chromosome determined for a normal cell

Filed: June 7, 1995

Marked-Up Version Of The Amended Claims

Page 16 [Exhibit A To Second Supplemental Amendment (Following Applicants'

June 14, 2001 Amendment For The Purpose Of Claim Consolidation)

-- July 12, 2001]

containing said particular chromosome, and determining whether the number of copies of said particular chromosome in said cell is abnormal.

1708. (Twice Amended) A process for identifying a chromosome of interest in a cell containing other chromosomes, the process comprising the steps of:

providing a set of clones or DNA fragments, or oligo- or polynucleotides derived from said clone or clones, wherein said clones or fragments or oligo- or polynucleotides are specifically hybridizable to a locus or loci in said chromosome of interest, wherein said clones or fragments or oligo- or polynucleotides comprise one or more detectable modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said modified or labeled nucleotides or nucleotide analogs are selected from the group consisting of:

- (i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a [radioactive] metal or metal ion and providing a

Filed: June 7, 1995

Marked-Up Version Of The Amended Claims

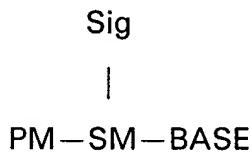
Page 17 [Exhibit A To Second Supplemental Amendment (Following Applicants'

June 14, 2001 Amendment For The Purpose Of Claim Consolidation)

-- July 12, 2001]

detectable [radioactive] signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof, and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;

(ii) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a [radioactive] metal or metal ion and providing a detectable [radioactive] signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached SM directly or through a linkage group; and

Filed: June 7, 1995

Marked-Up Version Of The Amended Claims

Page 18 [Exhibit A To Second Supplemental Amendment (Following Applicants'

June 14, 2001 Amendment For The Purpose Of Claim Consolidation)

-- July 12, 2001]

(iii) a nucleotide or nucleotide analog having the formula

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a [radioactive] metal or metal ion and providing a detectable [radioactive] signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

fixing the chromosomes from or in said cell;

contacting said fixed chromosomes under hybridizing conditions with said set of clones or DNA fragments or oligo- or polynucleotides, permitting specific hybridization of said set of clones or DNA fragments or oligo- or polynucleotides to said locus or loci in said chromosome of interest;

detecting [radioactively] by means of a [radioactive] metal or metal ion chelated by said chelating compound or chelating component any signal generated by each of said clones or DNA fragments or oligo- or polynucleotides which have specifically hybridized to said locus or loci in said chromosome of interest, and

Filed: June 7, 1995

Marked-Up Version Of The Amended Claims

Page 19 [Exhibit A To Second Supplemental Amendment (Following Applicants'

June 14, 2001 Amendment For The Purpose Of Claim Consolidation)

-- July 12, 2001]

obtaining a pattern of hybridizations between said set of clones or DNA fragments or oligo- or polynucleotides and said chromosomes; and

identifying said chromosome of interest by means of said hybridization pattern obtained.

1709. (Twice Amended) A process for identifying a plurality or all of the chromosomes in a cell of interest, the process comprising the steps of:

providing sets of clones or DNA fragments, or oligo- or polynucleotides derived from said clones, wherein each of said set of clones or DNA fragments or oligo- or polynucleotides are specifically hybridizable to a locus or loci in a chromosome of said cell of interest, wherein each of said clones or DNA fragments or oligo- or polynucleotides in said sets are labeled with a different indicator molecule and each of said clones or DNA fragments or oligo- or polynucleotides comprise one or more detectable modified or labeled nucleotides or nucleotide analogs capable of detection, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said modified or labeled nucleotide or nucleotide analogs are selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

Filed: June 7, 1995

Marked-Up Version Of The Amended Claims

Page 20 [Exhibit A To Second Supplemental Amendment (Following Applicants'

June 14, 2001 Amendment For The Purpose Of Claim Consolidation)

-- July 12, 2001]

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a [radioactive] metal or metal ion and providing a detectable [radioactive] signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE at a position other than the C5 position when BASE is a pyrimidine, or a pyrimidine analog, at a position other than the C8 position when BASE is a purine or a purine analog, and at a position other than the C7 position when BASE is a 7-deazapurine or a 7-deazapurine analog thereof;

(ii) a nucleotide or nucleotide analog having the formula

Sig

|

PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a [radioactive] metal or metal ion and providing a

Filed: June 7, 1995

Marked-Up Version Of The Amended Claims

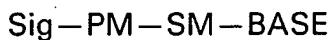
Page 21 [Exhibit A To Second Supplemental Amendment (Following Applicants'

June 14, 2001 Amendment For The Purpose Of Claim Consolidation)

-- July 12, 2001]

detectable [radioactive] signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a [radioactive] metal or metal ion and providing a detectable [radioactive] signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

fixing the chromosomes from or in said cell;

contacting said fixed chromosomes under hybridizing conditions with said sets of clones or DNA fragments or oligo- or polynucleotides, and permitting specific hybridization of said sets of clones or DNA fragments or oligo- or polynucleotides to the locus or loci in said chromosomes; and

Filed: June 7, 1995

Marked-Up Version Of The Amended Claims

Page 22 [Exhibit A To Second Supplemental Amendment (Following Applicants'

June 14, 2001 Amendment For The Purpose Of Claim Consolidation)

-- July 12, 2001]

detecting [radioactively] by means of a [radioactive] metal or metal ion chelated by said chelating compound or chelating component any signal generated by each of said different indicator molecules in said sets of clones or DNA fragments or oligo- or polynucleotides which have specifically hybridized to the locus or loci in said chromosomes, and identifying any one of the chromosomes in said cell of interest.

1710. (Twice Amended) A process for determining the number of chromosomes in an interphase cell of interest, the process comprising the steps of:

providing sets of clones or DNA fragments, or oligo- or polynucleotides derived from said clones, wherein each of said set of clones or DNA fragments or oligo- or polynucleotides are specifically complementary to or specifically hybridizable with at least one locus or loci in a chromosome of said interphase cell of interest, wherein each of said clones or DNA fragments or oligo- or polynucleotides in said sets comprise one or more detectable modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said modified or labeled nucleotide or nucleotide analog are selected from the group consisting of:

- (i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

Filed: June 7, 1995

Marked-Up Version Of The Amended Claims

Page 23 [Exhibit A To Second Supplemental Amendment (Following Applicants'

June 14, 2001 Amendment For The Purpose Of Claim Consolidation)

-- July 12, 2001]

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a [radioactive] metal or metal ion and providing a detectable [radioactive] signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE at a position other than the C5 position when BASE is a pyrimidine moiety or a pyrimidine analog, at a position other than the C8 position when BASE is a purine or a purine analog, and at a position other than the C7 position when BASE is a 7-deazapurine or a 7-deazapurine analog;

(ii) a nucleotide or nucleotide analog having the formula

Sig

|

PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a [radioactive] metal or metal ion and providing a

Filed: June 7, 1995

Marked-Up Version Of The Amended Claims

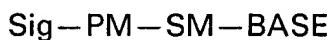
Page 24 [Exhibit A To Second Supplemental Amendment (Following Applicants'

June 14, 2001 Amendment For The Purpose Of Claim Consolidation)

-- July 12, 2001]

detectable [radioactive] signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached SM directly or through a linkage group; and

(iii) a nucleotide or nucleotide analog, said nucleotide having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a [radioactive] metal or metal ion and providing a detectable [radioactive] signal, wherein PM is covalently attached to the SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

contacting said interphase cell under hybridizing conditions with said sets of clones or DNA fragments or oligo- or polynucleotides, and permitting specific hybridization of said sets of clones or DNA fragments or oligo- or polynucleotides to any of the locus or loci in said chromosomes;

Filed: June 7, 1995

Marked-Up Version Of The Amended Claims

Page 25 [Exhibit A To Second Supplemental Amendment (Following Applicants'

June 14, 2001 Amendment For The Purpose Of Claim Consolidation)

-- July 12, 2001]

detecting [radioactively] by means of a [radioactive] metal or metal ion chelated by said chelating compound or chelating component any signals generated by each of said sets of clones or DNA fragments or oligo- or polynucleotides specifically hybridized to the locus or loci in said chromosomes, to obtain a pattern of generated signals; and comparing each generated signal with other generate signals in said pattern, and determining the number of chromosomes in said interphase cell of interest.

1711. (Twice Amended) A process for preparing a labeled oligo- or polynucleotide of interest, comprising the steps of:

(A) providing either:

(1) one or more detectable chemically modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA or an oligo- or polynucleotide of interest, alone or in conjunction with one or more other modified or unmodified nucleic acids selected from the group consisting of nucleotides, oligonucleotides and polynucleotides, wherein said other modified or unmodified nucleic acids are capable of incorporating into an oligo- or polynucleotide of interest, and wherein said chemically modified or labeled nucleotides or nucleotide analogs comprise one or more signaling moieties comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, or

Filed: June 7, 1995

Marked-Up Version Of The Amended Claims

Page 26 [Exhibit A To Second Supplemental Amendment (Following Applicants'

June 14, 2001 Amendment For The Purpose Of Claim Consolidation)

-- July 12, 2001]

(2) an oligo- or polynucleotide of interest comprising one or more of said detectable chemically modified or labeled nucleotides or nucleotide analogs, alone or in conjunction with one or more other modified or unmodified nucleic acids selected from the group consisting of nucleotides, oligonucleotides and polynucleotides,

wherein said chemically modified or labeled nucleotides or nucleotide analogs are modified on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate [moiety] analog, the base moiety or the base analog, and are selected from the group consisting of:

(i)

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a [radioactive] metal or metal ion and providing a detectable [radioactive] signal, and

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE directly or through a linkage group at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or

Filed: June 7, 1995

Marked-Up Version Of The Amended Claims

Page 27 [Exhibit A To Second Supplemental Amendment (Following Applicants'

June 14, 2001 Amendment For The Purpose Of Claim Consolidation)

-- July 12, 2001]

an analog thereof, and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;

(ii)

Sig

|

PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a [radioactive] metal or metal ion and providing a [radioactive] signal, and wherein said PM is covalently attached to SM, said BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii)

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a [radioactive] metal or metal ion and providing a

Filed: June 7, 1995

Marked-Up Version Of The Amended Claims

Page 28 [Exhibit A To Second Supplemental Amendment (Following Applicants'

June 14, 2001 Amendment For The Purpose Of Claim Consolidation)

-- July 12, 2001]

detectable [radioactive] signal; and wherein PM is covalently attached to SM, BASE is covalently attached SM, and Sig is covalently attached to PM directly or through a linkage group, provided that when said nucleotide or nucleotide analog (iii) is attached to an oligoribonucleotide or a polyribonucleotide, and provided that when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a [2',3'] 2', 3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide; and said oligo- or polynucleotide of interest; and

(B) either incorporating said one or more modified or labeled nucleotides or nucleotide analogs (A)(1) into said oligo- or polynucleotide, and preparing a labeled oligo- or polynucleotide of interest, or preparing said oligo- or polynucleotide of interest from said oligo- or polynucleotide recited in step (A)(2) above.

* * * * *